A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

GDCh

www.angewandte.org

Accepted Article

Title: Conformationally-Inspired Total Syntheses of Ohmyungsamycins A and B and Structural Revision of Ohmyungsamycin B

Authors: Joonseong Hur, Jaebong Jang, Jaehoon Sim, Woo Sung Son, Hee-Chul Ahn, Tae Sung Kim, Yern-Hyerk Shin, Changjin Lim, Seungbeom Lee, Hongchan An, Seok-Ho Kim, Dong-Chan Oh, Eun-Kyeong Jo, Jichan Jang, Jeeyeon Lee, and Young-Ger Suh

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201711286
Angew. Chem. 10.1002/ange.201711286

Link to VoR: http://dx.doi.org/10.1002/anie.201711286
http://dx.doi.org/10.1002/ange.201711286

WILEY-VCH

10.1002/anie.201711286

WILEY-VCH

COMMUNICATION

Conformationally-Inspired Total Syntheses of Ohmyungsamycins A and B and Structural Revision of Ohmyungsamycin B

Joonseong Hur,[a] Jaebong Jang,[a] Jaehoon Sim,[a][b] Woo Sung Son,[b] Hee-Chul Ahn,[c] Tae Sung Kim,[d] Yern-Hyerk Shin,[e] Changjin Lim,[a][b] Seungbeom Lee,[a] Hongchan An,[a] Seok-Ho Kim,[b] Dong-Chan Oh,[e] Eun-Kyeong Jo,[d] Jichan Jang,[f] Jeeyeon Lee,[a] and Young-Ger Suh*[a][b]

Abstract: The first total syntheses of bioactive cyclodepsipeptides ohmyungsamycin A and B have been achieved. The key features of our synthesis involve the concise preparation of the linear cyclization precursor, which consists of *N*-methyl amides and non-proteinogenic amino acids, and a bent conformationally-inspired macrolactamization. The revised structure of ohmyungsamycin B was established by our synthesis. The cyclic core of the ohmyungsamycins that is responsible for the excellent *anti*-TB activity was also elucidated via our synthesis and biological evaluation of a chain-truncated variant of the ohmyungsamycins.

Non-ribosomal cyclic peptides[1] belong to a major class of macrocyclic molecules that possess a variety of biological activities.[2] As structurally complex cyclopeptides have been identified, many synthetic hurdles, such as the preparation of non-proteinogenic amino acid, *N*-methyl amide formation, and macrocyclization, have been overcome by synthetic chemists.[3] Recently, novel cyclodepsipeptides, ohmyungsamycins (OMSs) A (**1**) and B (**2**) have been reported from *Streptomyces* genus strain.[4] Both natural products share a cyclic peptide core that consists of ten L-amino acids including two non-proteinogenic (4MeO-L-Trp[4] and L-βHyPhe[2]) and four *N*-methylated amino acids. Both OMSs possess the L-Val[11]-L-Val[12] dipeptide side chain appended to the core macrocycle, and OMS-B (**2**) possesses an *N*,*N*-dimethyl valine rather than the terminal *N*-methyl valine of OMS-A (**1**), as shown in Figure 1. Primary screening of the biological activities of the OMSs revealed potent cytotoxicity against various cancer cell lines and antibacterial activities with a narrow spectrum.[4]

More recently, the Pauli group identified ecumicin (**3**), which interestingly shares the same cyclic core as the OMSs.[5] The side chain of antituberculotic (*anti*-TB) ecumicin[6] possesses a non-ribosomal amino acid (*N*Me-L-*allo*-Ile[11]), which is extended to the side chain of OMS-B. Recently, OMSs were reported to exhibit strong *anti*-TB activity based on promotion of host cell autophagy,[7] which is an innate immune system targeting intracellular bacteria,[8] via an AMP-activated protein kinase pathway activation.

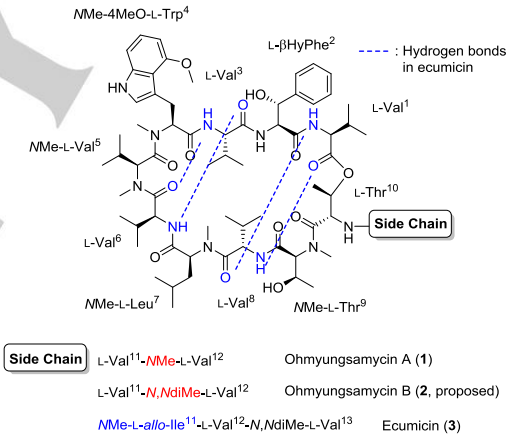


Figure 1. Reported structures of ohmyungsamycins A and B and ecumicin.

Based on the unique structural features and interesting biological activities of OMS-A and OMS-B, we have been interested in establishing a synthetic route to these macrolactams. Herein, we report the first total syntheses of OMS-A (**1**) and OMS-B (**2**; proposed structure) as well as the structural revision of OMS-B. In addition, we elucidated the core of the OMSs that is responsible for the biological activities based on our synthesis and biological evaluation of the side chain-truncated OMS (**4**; Δ[10]*N*-Ac ohmyungsamycin).

Our retrosynthetic analysis is outlined in Figure 2. We envisioned that OMS-B (**2**) could be obtained from OMS-A (**1**) by chemoselective and reductive methylation of the terminal monomethylamine. We paid special attention to the macrocyclization site,[9] because OMSs are highly congested with bulky amino acids including Val, Leu, 4MeO-Trp, and *N*-methyl amino acids. Structures of OMSs with only L-form amino acids

[a] J. Hur, Dr. J. Jang, Dr. J. Sim, Dr. C. Lim, Dr. S. Lee, Dr. H. An, Prof. Dr. J. Lee, Prof. Dr. Y.-G. Suh
College of Pharmacy, Seoul National University
1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea
E-mail: ygsuh@snu.ac.kr / ygsuh@cha.ac.kr
[b] Dr. J. Sim, Prof. Dr. W. S. Son, Dr. C. Lim, Prof. Dr. S.-H. Kim, Prof. Dr. Y.-G. Suh
College of Pharmacy, CHA University
120 Haeryong-ro, Pocheon, Gyeonggi-do 11160, Republic of Korea
[c] Prof. Dr. H.-C. Ahn
Department of Pharmacy, Dongguk University
Dongguk-ro 32, Ilsandong-gu, Goyang, Geonggi-do 10326, Republic of Korea
[d] Dr. T. S. Kim, Prof. Dr. E.-K. Jo
Department of Microbiology
Chungnam National University School of Medicine
Munhwa-ro 266, Jungku, Daejeon 35015, Republic of Korea
[e] Y.-H. Shin, Prof. Dr. D.-C. Oh
Natural Products Research Institute, College of Pharmacy,
Seoul National University
1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea
[f] Prof. Dr. J. Jang
Division of Applied Life Science, Research Institute of Life Science
Gyeongsang National University, Jinju 52828, Republic of Korea

Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201711286

may also limit the key macrocyclization.[9, 10] Importantly, the solid-state 3D structure of ecumicin (**3**) revealed a twisted β-sheet in the cyclic core, which was stabilized by four interstrand hydrogen bonds and two n→π* interactions (Figure 1).[11] Based on these conformation-stabilizing factors, we considered the four amino acid sequence from Val^3 to Val^6 as a potential turn inducer, which may induce an overall bent conformation in the linear cyclization precursor.[12] Based on the structural similarity between ecumicin and the OMSs, we anticipated that the conformational character of the cyclic core could be utilized in the syntheses of OMSs.

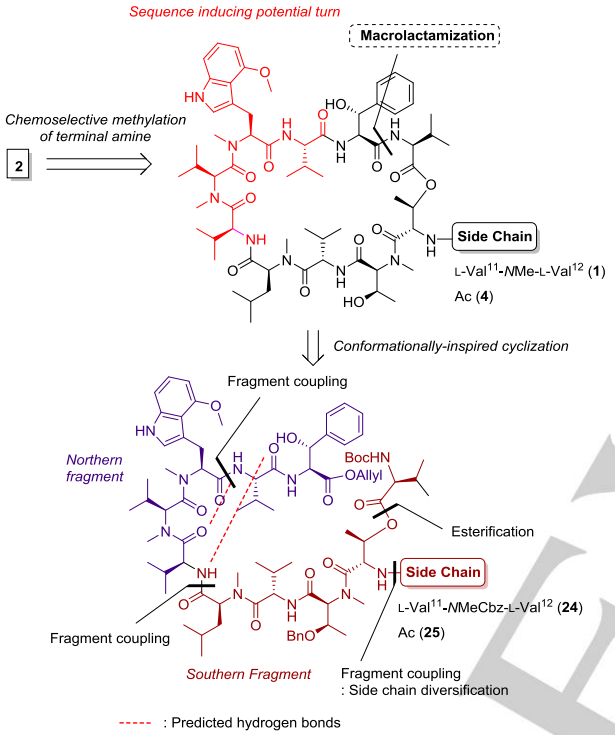
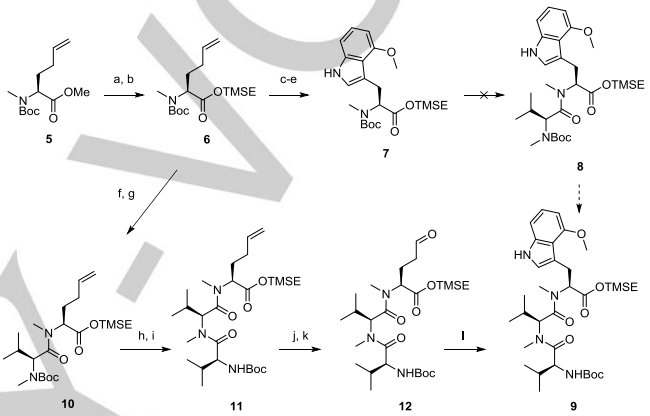


Figure 2. Retrosynthetic analysis of ohmyungsamycins A and B.

Therefore, we selected the cyclization site opposite to the potential turn inducer which may exploit the folded structure for the macrocyclization. Esterification of Val^1 and Thr^{10} and *N*-methyl amide formation of Thr^9 and Thr^{10} were precluded due to the low reactivity in the macrocyclization.[9, 13a] Amidation of Val^8 and Thr^9 was also not considered due to potential steric hindrance caused by inevitable protection of the Thr^9 hydroxyl group during the synthesis of the southern fragment. Therefore, we focused on amidation of Val^1 and $\beta HyPhe^2$, which appeared to be the most suitable ring-closing site. Indeed, macrocyclizations by esterification or amidation at other sites were not successful or provided the desired product in low yield (Scheme S1-S3). We planned to extend the side chain during the preparation of the southern part to avoid possible intramolecular *O* to *N* acyl shift[13] even though direct attachment of the side chain to the macrocyclic core would be ideal for further modifications.

Synthesis of the 4MeO-L-Trp containing tripeptide **9**, which is the most sterically encumbered fragment, is shown in Scheme 1. To incorporate the methoxy substituted indole ring moiety, we adopted palladium-catalyzed annulation.[14] Initially, the known homoallylglycine methyl ester **5**[14c] was converted to the bulky 2-(trimethylsilyl)ethyl (TMSE) ester **6** (77% for two steps) to avoid facile 2,5-diketopiperazine (DKP) formation[15] during the second amidation. Unfortunately, the 4MeO-Trp intermediate **7** did not undergo amidation with valine, which is most likely due to high steric hindrance. Therefore, homoallylglycine **6** was first converted to tripeptide **11** with the assistance of DEPBT[16] (49% for four steps) and then sequential dihydroxylation and oxidative cleavage of the terminal olefin of **11** followed by $Pd(OAc)_2$ catalyzed annulation of the resulting aldehyde **12** afforded tripeptide **9** possessing the 4MeO-indole moiety in 59% yield.



Scheme 1. Reagents and conditions: a) LiOH, THF/H_2O; b) TMSEOH, EDC, DMAP, CH_2Cl_2, 77% for 2 steps, c) 0.1 M OsO_4 in toluene, NMO, THF/H_2O; d) $NaIO_4$, THF/H_2O; e) 2-iodo-3-methoxyaniline, $Pd(OAc)_2$, DABCO, DMF, 100 °C 48% for 3 steps, f) TFA, CH_2Cl_2; g) Boc-*N*Me-L-Val-OH, DEPBT, DIPEA, CH_2Cl_2, 69% for 2 steps, h) TFA, CH_2Cl_2; i) Boc-L-Val-OH, DEPBT, DIPEA, CH_2Cl_2, 71% for 2 steps, j) 0.1 M OsO_4 in toluene, NMO, THF/H_2O; k) $NaIO_4$, THF/H_2O, 90% for 2 steps, l) 2-iodo-3-methoxyaniline, $Pd(OAc)_2$, DABCO, DMF, 100 °C, 59%.

With the tripeptide fragment **9** in hand, we turned our attention to the synthesis of tetrapeptide fragment **16** as shown in Scheme 2. To avoid facile DKP formation upon sequential elongation from the *C*-terminal *N*Me-Leu^7 residue, we prepared tripeptide **15** from Boc-*N*Me-L-Thr(OBn)-OH **13** (63% for three steps) under the optimized coupling conditions. Deprotection of **15** and DEPBT mediated coupling of the resulting free acid with H-*N*Me-L-Leu-OAllyl provided tetrapeptide **16** in 83% yield for the two steps.

The syntheses of cyclopeptides **1**, **2**, and **4** are described in Scheme 3. Dipeptides **17** and **19** were conveniently prepared via a standard peptide coupling procedure. The northern pentapeptide **18** was easily assembled in 95% yield by deprotection of tripeptide **9** and dipeptide **17** followed by a DEPBT-mediated amidation. Interestingly, the ^{1}H-NMR spectra revealed that the rotarmeric mixture of tripeptide **9**, which consisted of contiguous *N*-methyl amides, became a single isomer **18**. In addition to this observation, the hydrogen-deuterium exchange experiments[17] and molecular modeling based on the exchange experiments and NOE study (See supporting information) implied the turn-inducing effect of pentapeptide **18**, as shown in Scheme 3, in the solution state as previously mentioned in the retrosynthesis.

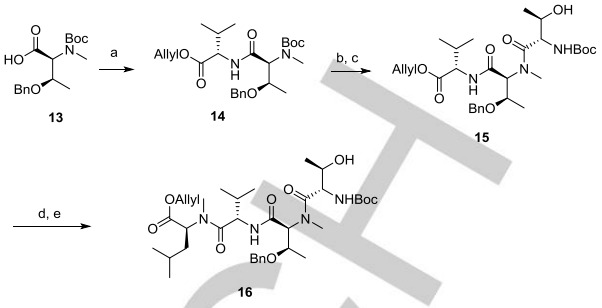
10.1002/anie.201711286

COMMUNICATION

The free amine prepared by Boc-deproptection of **16** and the free acid liberated from **19** by allyl-deprotection was coupled by DEPBT-mediated amidation to afford hexapeptide **20** in 72% overall yield from **16**. Independently, the structural variation of the southern part was carried out by introducing a new side chain on Thr[10]. Amidation of the free amine prepared from **16** by Ac_2O treatment in DMF provided tetrapeptide **21** in 68% yield from **16**. Esterification of hydroxyl peptides **20** and **21** with Boc-Val-OH smoothly proceeded under the reaction conditions (i.e., EDC, DMAP, and HOAt in CH_2Cl_2) to afford **22** in 97% yield and **23** in 98% yield, respectively.

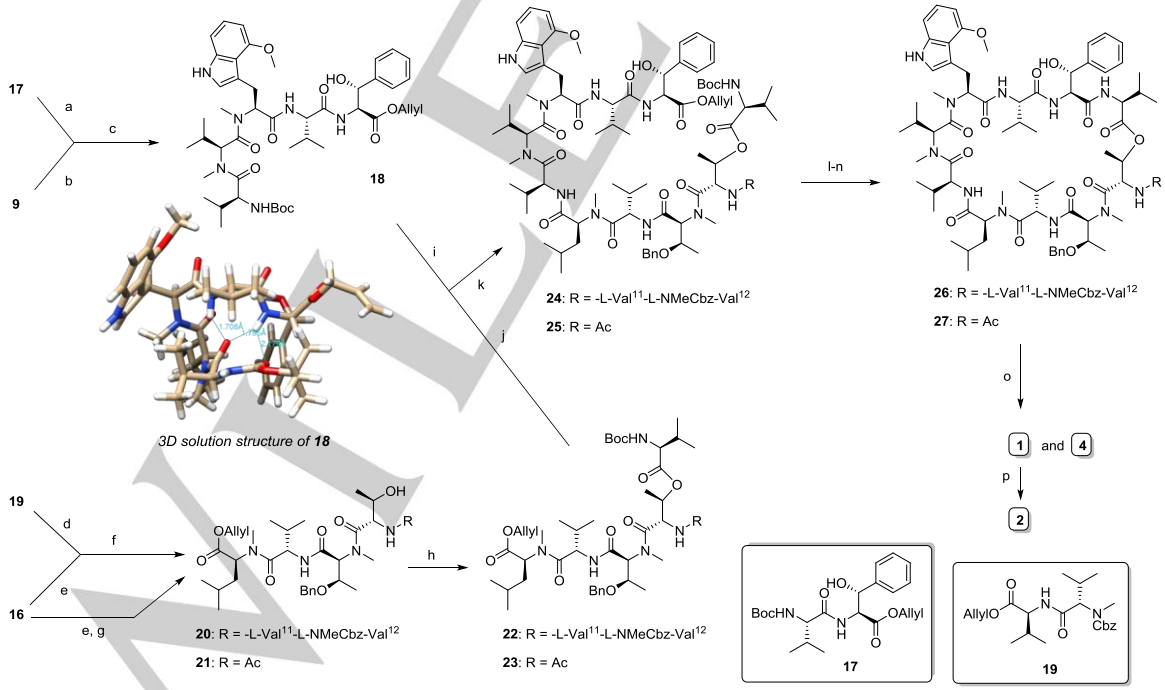
The final fragment assembly for the full-length dodecapeptide **24** suffered from rapid epimerization at the C_α position of Leu[7].[9a] Based on examination of a variety of coupling conditions, we finally obtained **24** in 56% yield along with *epi*-**24** by portionwise addition of EDC into a mixture of deprotected **18** and **22**, DIPEA, and HOAt in CH_2Cl_2 at 0 °C. Decapeptide **25** was prepared under the same reaction conditions as **24** in 50% yield.

Allyl deprotection of **24** and **25** with Pd(0) and PhNHMe followed by careful Boc-deprotection with *i*Pr_3SiH in TFA/CH_2Cl_2 (1:10) afforded the corresponding amino-acid TFA salts, which were subjected to macrocyclization under high-dilution conditions (0.5 mM).[18] Dichloromethane was crucial for successful ring closure. The cyclodimer and cyclotrimer were produced regardless of the coupling reagent (e.g., EDC, HATU, PyBOP and DEPBT) when DMF was used as a solvent, which was most likely due to the high dielectric solvent preventing the formation of the hydrogen bonding-induced bent conformation.[19]



Scheme 2. Reagents and conditions: a) H-L-Val-OAllyl, EDC, DIPEA, Oxyma, DMF, 93%, b) TFA, CH_2Cl_2; c) Boc-L-Thr-OH, HATU, DIPEA, HOAt, DMF, 67% for 2 steps, d) $Pd(PPh_3)_4$, PhNHMe, THF; e) H-*N*Me-L-Leu-OAllyl, DEPBT, DIPEA, CH_2Cl_2, 83% for 2 steps.

After intensive optimization of the macrolactamization conditions, the desired cyclopeptide **26** was obtained in 42% yield for three steps via slow addition of the linear substrate into a CH_2Cl_2 solution containing PyBOP and DIPEA. Cyclization of **25** proceeded more smoothly to afford cyclopeptide **27** in 69% yield for three steps. The increased yield was likely due to the reduced steric effect of the side chain. Finally, hydrogenolytic deprotection of **26** and **27** produced OMS-A (**1**) and the side chain-truncated OMS (**4**) in 97% and 68% yield, respectively. For the synthesis of OMS-B (**2**), a new methyl substituent was directly introduced onto the terminal amine of **1** via reductive methylation[20] in 71% yield.



Scheme 3. Reagents and conditions: a) TFA, CH_2Cl_2; b) TBAF, THF; c) DEPBT, DIPEA, CH_2Cl_2, 95% from **9**, d) $Pd(PPh_3)_4$, PhNHMe, THF; e) TFA, CH_2Cl_2; f) DEPBT, DIPEA CH_2Cl_2, 72% from **16**, g) Ac_2O, DMF, 68% from **16**, h) Boc-L-Val-OH, EDC, DMAP, HOAt, CH_2Cl_2, 97% for **22**, 98% for **23**, i) TFA, CH_2Cl_2; j) $Pd(PPh_3)_4$, PhNHMe, THF; k) EDC, DIPEA, HOAt, CH_2Cl_2, 56% for **24**, 50% for **25**, l) $Pd(PPh_3)_4$, PhNHMe, THF; m) TFA, *i*Pr_3SiH, CH_2Cl_2; n) PyBOP, DIPEA, CH_2Cl_2 (0.5 mM), 42% for **26**, 69% for **27**, o) $Pd(OH)_2$, H_2, MeOH, 97% for **1**, 68% for **4**, p) aq. HCHO, $NaBH_3CN$, DMF/AcOH (10:1), 71%

10.1002/anie.201711286

All spectroscopic data of synthetic OMS-A (**1**) were exactly matched with the reported data. The structure of the new cyclopeptide **4** was also confirmed by careful analysis of the spectral data. Importantly, the $J_{H\text{-}H}$ coupling constants and major through-space correlation measured by the ROESY experiment were consistent with the reported data for **1**,[4] supporting the role of the cyclic core in maintaining a stable 3D structure regardless of the side chain (Table S2 and Figure S3).

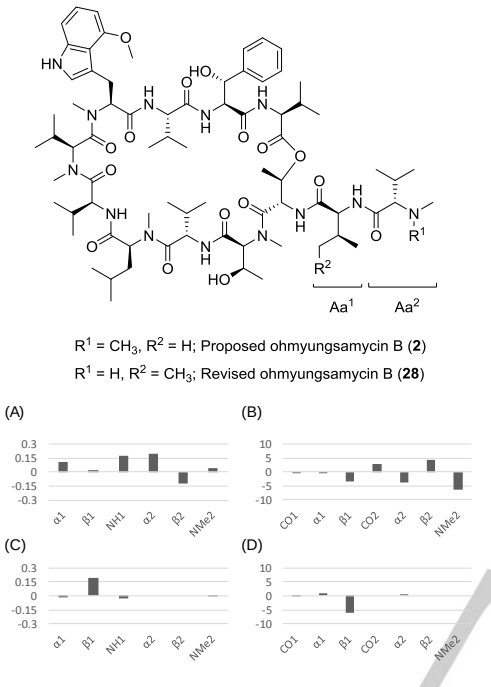
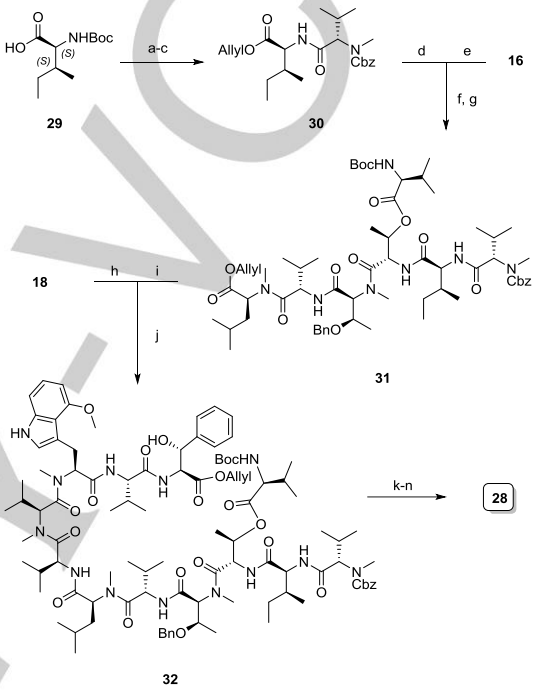


Figure 3. Chemical structure of the proposed and revised OMS-B (top, Aa: amino acid). Side chain chemical shift comparison between OMS-A and natural or synthetic OMS-B (bottom). (A) Comparison of ^{1}H NMR spectra for OMS-A (**1**) and synthetic OMS-B (**2**); (B) Comparison of ^{13}C NMR spectra for OMS-A (**1**) and synthetic OMS-B (**2**); (C) Comparison of ^{1}H NMR spectra for OMS-A (**1**) and natural OMS-B; (D) Comparison of ^{13}C NMR spectra for OMS-A (**1**) and natural OMS-B. Y axis indicates $\Delta\delta$ (OMS-A – OMS-B, ppm)

Unexpectedly, the spectral data of the synthetic OMS-B (**2**) were not identical to those of natural OMS-B, except for the mass spectroscopic data. In particular, the ^{1}H and ^{13}C NMR spectra corresponding to the side chain were quite different (Table S3 and Figure S4). As shown in Figure 3, a comparison of the spectral data for the natural OMS-A with those to the synthetic (Figure 3A and 3B) and natural OMS-B (Figures 3C and 3D) revealed significantly different chemical shifts for the synthetic OMS-B. This result was likely due to a difference in the electron donating effect, which depends on the position of methyl substituent. Therefore, we assumed that the additional methyl substituent involved in isoleucine as the 11th amino acid based on intensive analysis of the 1D and 2D NMR spectra as well as the COSY and e-HSQC data (see Supporting Information). Among the four possible diastereomers of isoleucine, we selected the naturally abundant L-Ile. Synthesis of the structurally revised OMS-B readily proceeded under the previously optimized conditions to afford **28** in 6% overall yield from Boc-L-Ile as outlined in Scheme 4. To our delight, the spectral data of this synthetic OMS-B (**28**) matched the reported data (Table S4 and Figure S9). We further confirmed the absolute configuration of Ile in natural OMS-B by the HPLC analysis of GITC[21] (2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate) derivatives of Ile in natural OMS-B and authetic L-Ile, L-*allo*-Ile, D-Ile, and D-*allo*-Ile (Figure S10).



Scheme 4. Reagents and conditions: a) AllylBr, K_2CO_3, DMF; b) TFA, CH_2Cl_2; c) Cbz-*N*Me-L-Val-OH, EDC, DIPEA, HOAt, CH_2Cl_2, 68% for 3 steps, d) $Pd(PPh_3)_4$, PhNHMe, THF; e) TFA, CH_2Cl_2; f) DEPBT, DIPEA CH_2Cl_2, g) Boc-L-Val-OH, EDC, DMAP, HOAt, CH_2Cl_2, 66% from **16**, h) TFA, CH_2Cl_2; i) $Pd(PPh_3)_4$, PhNHMe, THF; j) EDC, DIPEA, HOAt, CH_2Cl_2, 36% from **31**, k) $Pd(PPh_3)_4$, PhNHMe, THF; l) TFA, *i*Pr_3SiH, CH_2Cl_2; m) PyBOP, DIPEA, CH_2Cl_2 (0.5 mM) 39% for three steps, n) $Pd(OH)_2$, H_2, MeOH, 90%

After complete syntheses of OMS-A (**1**), Δ^{10}*N*-Ac OMS (**4**), and structurally revised OMS-B (**28**), we evaluated their *anti*-TB activities, which are summarized in Table 1. As expected, the synthetic OMS-A exhibited nearly the same potency (MIC_{50}: 33.3 nM) compared to the previously reported one (MIC_{50}: 57 nM).[7] Interestingly, both the proposed (**2**) and revised OMS-B (**28**) exhibited comparable *anti*-TB activities. It is important to note that the side chain-truncated OMS-A (**4**) also exhibited good *anti*-TB activity (MIC_{50}: 740 nM), which is still more potent than ethambutol (MIC_{50}: 3.1 μM). These results support the crucial role of the cyclic core for *anti*-TB activity as well as the significant beneficial effects of the side chain.

In conclusion, we have accomplished the first total syntheses of ohmyungsamycins A (**1**) and B (**28**), the side chain-truncated ohmyungsamycin B (**2** to **28**). The key macrocyclization strategy

Table 1. *Anti*-TB activities of the ohmyungsamycins and structurally relevant cyclopeptides

Compound	MIC_{50}
OMS-A (**1**)	33.3 nM
OMS-B; proposed (**2**)	64.9 nM
OMS-B; revised (**28**)	108.3 nM
Δ^{10}N-Ac OMS (**4**)	740 nM
Ethambutol	3.1 μM

for the syntheses of the OMSs was inspired by the conformation of the cyclic core. In addition, synthesis of the side chain-truncated ohmyungsamycin A enabled the elucidation of the core of ohmyungsamycins, which is responsible for the excellent *anti*-TB activities. Our convergent syntheses of the ohmyungsamycins can be widely utilized by synthetic and medicinal chemists.

Acknowledgements

This work was supported by the National Research Foundation of Korea grant funded by the Ministry of Science and ICT of Korea (2009-0083533) and by the GRRC program of Gyeonggi province (GRRC-CHA2017-B02).

Keywords: cyclodepsipeptide • total synthesis • natural products • macrolactamization • structural revision

[1] D. Schwarzer, R. Finking, M. A. Marahiel, *Nat. Prod. Rep*. **2003**, *20*, 275.

[2] E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug. Discov.* **2008**, *7*, 608.

[3] a) Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441; b) W. Li, A. Schlecker, D. Ma, *Chem. Commun.* **2010**, *46*, 5403; c) A. Guzman-Martinez, R. Lamer, M. S. VanNieuwenhze, *J. Am. Chem. Soc.* **2007**, *129*, 6017-6021; d) W. Jiang, J. Wanner, R. J. Lee, P. Y. Bounaud, D. L. Boger, *J. Am. Chem. Soc.* **2003**, *125*, 1877; e) L. Tan, D. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 3614; f) M. Pelay-Gimeno, F. Albericio, J. Tulla-Puche, *Nat. Protocols* **2016**, *11*, 1924; g) G. Yao, Z. Pan, C. Wu, W. Wang, L. Fang, W. Su, *J. Am. Chem. Soc.* **2015**, *137*, 13488; h) S. Fuse, H. Koinuma, A. Kimbara, M. Izumikawa, Y. Mifune, H. He, K. Shin-ya, T. Takahashi, T. Doi, *J. Am. Chem. Soc.* **2014**, *136*, 12011.

[4] S. Um, T. J. Choi, H. Kim, B. Y. Kim, S. H. Kim, S. K. Lee, K. B. Oh, J. Shin, D. C. Oh, *J. Org. Chem.* **2013**, *78*, 12321.

[5] W. Gao, J. Y. Kim, S. N. Chen, S. H. Cho, J. Choi, B. U. Jaki, Y. Y. Jin, D. C. Lankin, J. E. Lee, S. Y. Lee, J. B. McAlpine, J. G. Napolitano, S. G. Franzblau, J. W. Suh, G. F. Pauli, *Org. Lett.* **2014**, *16*, 6044.

[6] W. Gao, J. Y. Kim, J. R. Anderson, T. Akopian, S. Hong, Y. Y. Jin, O. Kandror, J. W. Kim, I. A. Lee, S. Y. Lee, J. B. McAlpine, S. Mulugeta, S. Sunoqrot, Y. Wang, S. H. Yang, T. M. Yoon, A. L. Goldberg, G. F. Pauli, J. W. Suh, S. G. Franzblau, S. Cho, *Antimicrob. Agents Chemother.* **2015**, *59*, 880.

[7] T. S. Kim, Y.-H. Shin, H.-M. Lee, J. K. Kim, J. H. Choe, J.-C. Jang, S. Um, H. S. Jin, M. Komatsu, G.-H. Cha, H.-J. Chae, D.-C. Oh, E.-K. Jo, *Sci. Rep.* **2017**, *7*, 3431.

[8] J. Huang, J. H. Brumell, *Nat. Rev. Micro.* **2014**, *12*, 101.

[9] a) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243; b) C. J. White, A. K. Yudin, *Nat. Chem.* **2011**, *3*, 509;

[10] a) D. Birch, M. North, R. R. Hill, G. E. Jeffs, *Chem. Commun.* **1999**, 941; b) S. F. Brady, S. L. Varga, R. M. Freidinger, D. A. Schwenk, M. Mendlowski, F. W. Holly, D. F. Veber, *J. Org. Chem.* **1979**, *44*, 3101; c) A. Ehrlich, H.-U. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino, M. Bienert, *J. Org. Chem.* **1996**, *61*, 8831.

[11] G. J. Bartlett, A. Choudhary, R. T. Raines, D. N. Woolfson, *Nat. Chem. Biol.* **2010**, *6*, 615.

[12] J. Blankenstein, J. Zhu, *Eur. J. Org. Chem.* **2005**, 1949.

[13] a) J. S. Davies, *J. Pept. Sci.* **2003**, *9*, 471; b) A. A. Tymiak, T. J. McCormick, S. E. Unger, *J. Org. Chem.* **1989**, *54*, 1149.

[14] a) C.-y. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676; b) Y. Jia, J. Zhu, *J. Org. Chem.* **2006**, *71*, 7826; c) P. Danner, M. Morkunas, M. E. Maier, *Org. Lett.* **2013**, *15*, 2474.

[15] a) M. C. Khosla, R. R. Smeby, F. M. Bumpus, *J. Am. Chem. Soc.* **1972**, *94*, 4721; b) T. Kuranaga, A. Enomoto, H. Tan, K. Fujita, T. Wakimoto, *Org. Lett.* **2017**, *19*, 1366.

[16] H. Li, X. Jiang, Y. Ye, C. Fan, T. Romoff, M. Goodman, *Org. Lett.* **1999**, *1*, 91.

[17] L. R. Steffel, T. J. Cashman, M. H. Reutershan, B. R. Linton, *J. Am. Chem. Soc.* **2007**, *129*, 12956.

[18] C. Galli, L. Mandolini, *J. Chem. Soc., Chem. Commun.* **1982**, 251.

[19] T. Rezai, B. Yu, G. L. Millhauser, M. P. Jacobson, R. S. Lokey, *J. Am. Chem. Soc.* **2006**, *128*, 2510.

[20] a) L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823; b) N. Jentoft, D. G. Dearborn, *Methods Enzymol*. **1983**, *91*, 570.

[21] S. Hess, K. R. Gustafson, D. J. Milanowski, E. Alvira, M. A. Lipton, L. K. Pannell, *J. Chromatogr. A* **2004**, *1035*, 211.

10.1002/anie.201711286

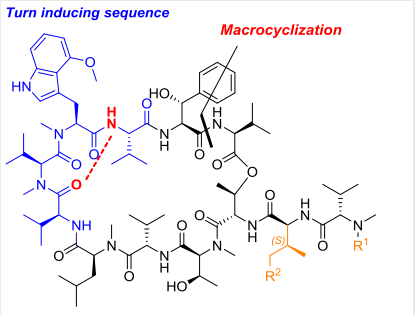
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

The first total syntheses of bioactive cyclodepsipeptides, ohmyungsamycins A and the proposed ohmyungsamycin B have been achieved. In addition, the proposed structure of ohmyungsamycin B was revised.



*Joonseong Hur, Jaebong Jang, Jaehoon Sim, Woo Sung Son, Hee-Chul Ahn, Tae Sung Kim, Yern-Hyerk Shin, Changjin Lim, SeungBeom Lee, Hongchan An, Seok-Ho Kim, Dong-Chan Oh, Eun-Kyeong Jo, Jichan Jang, Jeeyeon Lee, and Young-Ger Suh**

Page No. – Page No.

Conformationally-Inspired Total Syntheses of Ohmyungsamycins A and B and Structural Revision of Ohmyungsamycin B